

REMARKS

Status of the Claims

Claims 8-16 are pending. Claims 1-7, and 17-21 are canceled. Claims 8 and 10 are amended.

Turning now to the official Office Action, the following numbered paragraphs correspond to the numbered paragraphs of the Office Action

1. Jacoby Reference

For the convenience of the Examiner, the requested information regarding the Jacoby reference is submitted on a PTO Form 1449, attached.

2. Restriction Requirement

As stated in the Office Action, Applicants elected Group II, claims 8-16. The Species Election of February 24, 2002 was for the purposes of beginning the search and examination of Group II. Applicants respectfully submit that there is no applicable prior art that renders the species of Group II obvious or anticipated. Accordingly, Applicants assume that an expanded search of Group II will continue.

3-5. No remarks are required.

6. Claims 8, and 12-14 stand rejected under 35 U.S.C. § 112 as allegedly “being based on a specification which does not contain an adequate enabling written description of ‘X’ defined as ‘an organic compound capable of bonding to a detectable substance’”. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

With respect to the present invention, a “detectable substance” is an entity or group, the presence or absence of which in a material such as a biological material, is to be ascertained by use of the organo luminescent semiconductor nanocrystal probe of the present invention. The detectable substance is related^{to} the “affinity molecule” in that the term “affinity molecule” is the portion of the organo luminescent semiconductor nanocrystal probe of the present invention which will selectively bond to a detectable substance (if present) in the material (i.e., biological material) being analyzed.

Finally, one of ordinary skill in the art would understand that the biologically active compound is the detectable substance.

The above definitions are incorporated by reference from U.S. Patent No. 5,990,479 to Weiss et al. Such an amendment presents no new matter because the ‘479 patent is incorporated by reference in the Specification.

7. Claims 8-16 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not being enabled “for the preparation and use of nanocrystal compounds wherein an -S- moiety is present on the nanocrystal *per se*, as claimed, is directly substituted with an alkylene linker-drug moiety.

This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

More specifically, the Office Action alleges that the Specification only provides enablement for making and using nanocrystals that comprise a trioctylphosphine (TOPO) coating.

Applicants respectfully submit that it is well established that by law a patent application is presumptively enabled when filed. That is, during examination, “[a]s a matter of Patent Office practice... a specification... must be taken as in compliance with the enablement requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.” *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (CCPA 1971). Moreover,

...it is incumbent upon the Patent Office, whenever a rejection on [grounds of enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate statement.

not part

Id. At 369-70. Indeed, as pointed out by the U.S.P.T.O. in the *Section 112 Enablement Training Manual* (citing *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993)), “the case law makes it clear that properly reasoned and supported statements explaining any failure to comply with section 112 are a requirement to support a rejection.”

In the instant case, the Examiner has summarily alleged that there is no enablement with respect to making and using nanocrystal compounds without a TOPO coating. The rejection is

not supported by a technical journal or the like. Applicants respectfully submit that the literature of record, including that cited by the Examiner, suggests otherwise (in favor of enablement).

Without being bound by theory, one of ordinary skill in the art would understand that the TOPO coating, *inter alia*, may be present to help prevent nanocrystal precipitation, or to help prevent the nanocrystals from sticking together. The Examiner has not produced any evidence of the TOPO's required presence.

Accordingly, Applicants respectfully submit that this rejection be withdrawn.

8. Claim 11 stands rejected under 35 U.S.C. § 112, second paragraph as allegedly not being enabled. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Specifically, the Office Action alleges that the Specification is not enabling for one of ordinary skill in the art to make or use compounds where the point of attachment for the linker arm to the biologically active compound at a place on the benzene other than the 2-position. Claim 28 shows the point of attachment as being a variable point of attachment on the benzene ring.

As is discussed in the above paragraph, it is incumbent upon the Patent Office to support such a position, and show there is adequate grounds to make the rejection, with evidence such as a technical journal or the like.

As stated by the Federal Circuit, "[a] threshold issue is whether the PTO met its burden of proof in calling into question the enablement of applicant's disclosure." *In re Strahilevitz*, 212 U.S.P.Q. 561, 563 (CCPA 1982).

The test for enablement is not whether or not whether or not any experimentation is required. The test for enablement is whether or not the experimentation required is undue. See *In re Wright*, 27 U.S.P.Q.2d at 1513, (“Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples.”) A specification can still comply with the requirements of § 112 even if it leaves some technical problems unresolved, so long as one of ordinary skill in the art could resolve them in a reasonable time.

Courts have stressed that not every species encompassed by the claims, even in unpredictable arts, need to be disclosed. If § 112 required a disclosure of a test with every species covered by a claim even in an unpredictable art, then a prohibited number of actual experiments would have to be performed, discouraging the filing of patent applications in unpredictable areas. See *In re Angstadt*, 190 U.S.P.Q. 214, 218 (CCPA 1976).

There is nothing set forth in the Office Action to indicate that one of ordinary skill in the art could not attach the carbon as a substituent on the benzene ring at any available carbon position. Accordingly, Applicants respectfully request that this rejection be withdrawn.

9. Claims 8-16 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested. Each issues raised by the Office Action is discussed in turn, below.

(a). The Office Action states that “[i]t is unclear what is meant by the term ‘an organic compound capable of bonding to a detectable substance.’”

In view of the discussion in paragraph 6, above, and the amendment to the Specification, that this term is definite.

(b). The Office Action states that “[i]n claim 8, the non-terminal group ‘R₃’ is improperly defined as a terminal moiety ‘SH’”.

Applicants respectfully submit that R₃ is properly defined. Claim 25 is directed to a nanocrystal compound, with Y being defined as the nanocrystal. R₃ is part of the linker arm portion of the compound that is attached to the nanocrystal, Y. As such SH is properly defined.

(c). The Office Action states that Claim 10 is inconsistent with Claim 8. In view of the above amendment (R is the attachment point to R₂), this issue is believed to be moot.

(d). The Office Action states that it is unclear as to which moiety the -S- group is attached to the nanocrystal.

Applicants respectfully submit that the -S- group attaches to the surface of the nanocrystal. Sulfur is attached by electrostatic interactions in a manner similar to which thiols are attached to gold surfaces or nanoparticles. This is a common occurrence in the nanocrystal art. For example, see U.S. Patent Numbers 6,221,602 and 5,990,479 cited by Applicants and 6,306,610 cited by the Examiner.

In view of the above, Applicants respectfully submit that this rejection be withdrawn.

Structure
indicates
covalent
bond

10-11. Claims 8-10, and 12-25 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims in co-pending Application No. 09/864,731. This rejection is respectfully traversed.

However, the Examiner is requested to hold this rejection in abeyance until there is an indication of allowable subject matter in this application or in 09/864,731. This rejection should be withdrawn in the first application allowed.

12. Claims 8-16 stand rejected under the judicially created doctrine as being drawn to an improper Markush group. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The Markush group appearing in claim 8 is directed to a scientifically related group of nanocrystal compounds. That is, all of the compounds of the group have a common function as fluorescent tags capable of tracing specific substances within cells.

In any Markush group, it has been recognized that the compounds will differ from each other in certain respects. Applicants respectfully submit that these differences have varied widely in some respects, namely with respect to aliphatic, aromatic, and aralkyl compounds, which have been permitted to be grouped together.

The nanocrystal compounds of claim 8 comprise nanocrystals and linker arms (that in turn comprise an alkyl chain) that belong to a subgenus that is not repugnant to scientific classification.

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As an example, the Examiner's attention is respectfully directed to US Patent No. 5,990,479, which is incorporated by reference into the instant Application. Claim 1 of '479 is directed to a nanocrystal compound that comprises:

- (a) a semiconductor nanocrystal capable of emitting light in an narrow wavelength band when excited, and
- (b) one or more linking agent linked to said semiconductor nanocrystal and capable of linking to said affinity molecule.

Since it is clear that the Markush group of the present claims are directed to a recognized subgenus, share common structural features, and share a common function, Applicants submit that this rejection should be withdrawn.

13-14. Claims 8-16 stand rejected under 35 U.S.C. § 103 as allegedly being obvious over Bruckez et al., United States Patent No. 6,274,323; or Bawendi et al., United States Patent No. 6,306,610.

This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The '323 Patent discloses the use of semiconductor nanocrystals as detectable labels in various chemical and biological applications. This patent fails to disclose or suggest the nanocrystal compounds of the present invention that comprise a nanocrystal, polyether linker arm, and organic compound capable of bonding to a detectable substance (i.e., an affinity molecule).

The disclosure relied upon by the PTO in the Office Action is directed to compounds that attach to the surface of the nanocrystals that “*terminate in at least one hydrophilic moiety.*” See ‘323 at col. 21, line 67 – col. 22, line 2. The purpose of this compound is to impart water solubility to the nanocrystal. The Office Action specifically refers to “[e]xemplary hydrophilic groups [that] include... polyethers.”

One of ordinary skill in the art would certainly not be motivated to modify this disclosure to arrive at the present invention. That is, there is nothing in the references that would motivate one of ordinary skill in the art to modify the water-solubilizing compound of the reference to arrive at the linker arm portion of the claimed nanocrystal compound, and attach an organic compound capable of bonding to a detectable substance of the present invention.

The ‘609 Patent discloses fluorescent semiconductor nanocrystals associated to a compound. Likewise, this patent fails to disclose or suggest the nanocrystal compounds of the present invention that comprise a semiconducting nanocrystal, linker arm, and organic compound capable of bonding to a detectable substance.

The formula relied upon by the PTO in the Office Action is part of the “water-solubilizing layer.” See ‘610 at claim 1, as cited in the Office Action. Again, there is nothing in the references that would motivate one of ordinary skill in the art to modify the water-solubilizing compound of the reference to arrive at the linker arm portion of the claimed nanocrystal compound, and attach an organic compound capable of bonding to a detectable substance of the present invention.

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation *found within the reference* to modify the reference to arrive at the present invention

with a reasonable expectation of success. Also, the reference, when combined, must disclose or suggest all of the claimed features. For at least the reason stated above, there is no motivation found in either one of the cited references to modify the reference and add the claimed features.

Accordingly, Applicants respectfully submit that this rejection be withdrawn.

15. Claims 8-16 are rejected under 35 U.S.C. § 103 as allegedly being obvious over '323 and '610 cited above, further in combination with Zalipsky (Bioconjugate Chem) or Zalipsky (Eur. Polym. J.). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

The deficiencies of '323 and '610 are discussed above. These deficiencies are not remedied by the Zalipsky articles. The Zalipsky articles disclose the attachment of drugs to polyethylene glycols. The PEG is used as a carrier polymer for drugs such as penicillin, aspirin, amphetamine, etc. Zalipsky et al. state that PEG was chosen because:

it is known to be non-toxic, non-antigenic and biocompatible, to be soluble in water and organic solvents and by itself to have solubilizing properties.

It is not biodegradable and is available in a wide range of molecular weights. Because of these properties, it is widely used in biochemistry and molecular biology, and is commercially used in pharmacological products, cosmetics and food. It is therefore suitable for use as a drug carrier in the body.

see the Eur. Polym. J. article at page 1177.

Nanocrystals and nanocrystal technology related to labeling techniques are not discussed in the articles.

One of the requirements in establishing a *prima facie* case of obviousness is that the prior art relied upon must contain some suggestion or incentive that would have motivated the skilled artisan to combine the references in a way that would produce the claimed invention. See *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 58 U.S.P.Q. 1286, 1293 (Fed. Cir. 2001). That is, one of ordinary skill in the art cannot simply take various components and combine them without a commonality or purpose or characteristics that gives the artisan some reasonable expectation of success.

Applicants respectfully submit that there is nothing in the disclosures of the '610 or '323 patents that would suggest to one of ordinary skill in the art that a polyethylene glycol carrier can be modified and substituted for the water-solubilizing layer or water-solubilizing compound of the patents. Likewise, as stated above, there is nothing in the Zalipsky references that would lead one of ordinary skill in the art to attach a drug, for example, to a polyethylene glycol, then use that compound in connection with semiconductor nanocrystal labeling. There is no indication in the reference that the structures disclosed are even attachable to nanocrystals.

The Federal Circuit in *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988), insisted that "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art lead the individual to combine the relevant teachings of the references."

Applicants respectfully submit that there is no such objective support or explanation in the references as to why the suggested combination is desirable or would even work..

From the forgoing, further reconsideration in the form of a Notice of Allowability is requested and such action is believed to be in order.

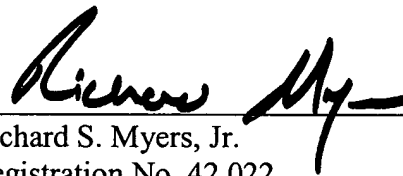
Petition for Extension of Time

Pursuant to the provisions of 37 C.F.R. §§ 1.17, 1.136(a), the Applicants hereby petition for an extension of time of two months to October 1, 2003 for the period in which to file a response to the outstanding Office Action. The required fee of \$205.00 is attached hereto.

Please charge any fees or credit any overpayment pursuant to 37 C.F.R. §§ 1.16, 1.17 to Deposit Account 502752.

Finally, if the Examiner has any questions concerning this election or the Application in general, she is respectfully requested to contact the undersigned at the number listed below.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Richard S. Myers, Jr.", is written over a horizontal line.

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